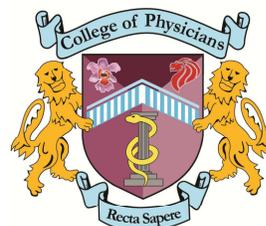




National Centre for
Infectious Diseases



CHAPTER OF INFECTIOUS DISEASE PHYSICIANS
COLLEGE OF PHYSICIANS, SINGAPORE

Interim Treatment Guidelines for COVID-19

(Version 3.0, dated 6 July 2020)

ABSTRACT

Background

In December 2019, pneumonia cases caused by a novel coronavirus occurred in Wuhan, Hubei Province. As of 11th February 2020, the World Health Organisation has officially named the disease “COVID-19”. and the causative agent, “SARS-CoV-2”. This guideline provides updated interim evidence-based recommendations on the therapeutic management of patients with COVID-19 in Singapore, from our initial guidance issued on 2 April 2020.

Methods

Published clinical trials, cohort studies, society and professional guidelines related to the treatment of COVID-19 were analysed, and where appropriate, selected pre-print data. Each recommendation was discussed by an expert committee and screened for conflicts of interest.

Recommendations

Results from several important studies for treatments for COVID-19 (remdesivir, lopinavir/ritonavir, combination regimen of interferon/lopinavir/ritonavir/ribavirin, hydroxychloroquine, and convalescent plasma, dexamethasone) have been made available since the last review. Emerging data also indicate a relative thrombophilic state in COVID-19. Based on available data, remdesivir, if available, is recommended for hospitalised patients with severe COVID-19 (i.e. SpO₂ <94% on room air, requiring supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). Lopinavir/ritonavir as a single agent is not likely to be effective in patients with more severe or late disease. Hydroxychloroquine is not recommended as therapy due to a lack of clear clinical benefit from available data and possible toxicity. Early data from expanded use programmes for convalescent plasma have not reported overt safety concerns, although further data is needed to define therapeutic benefit in COVID-19, as is the case with Interferon beta-1B (+/- lopinavir/ritonavir), IL-6 inhibitor and other immunomodulator therapies. Given the propensity for thromboembolic disease with COVID-19,

pharmacologic prophylaxis should be considered in critically ill patients who do not have contraindications. Early data on dexamethasone from the RECOVERY trial indicate a mortality benefit in patients receiving oxygen or on mechanical ventilation, however full trial results are awaited.

Conclusions

Remdesivir, where available, should be considered for patients with severe COVID-19 (including those who require supplemental oxygen or have a SpO₂ ≤94% on room air). Dexamethasone may be considered in patients with COVID-19 on oxygen or mechanical ventilation. Further data is awaited for IL-6 and other immunomodulatory therapies, interferon beta-based treatments, and convalescent plasma.

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1. Overview

Early supportive care and monitoring—including oxygen supplementation, organ support and prevention of complications, especially acute respiratory distress syndrome, organ failure and secondary nosocomial infections—remain the cornerstone and most important management strategy for clinical management of COVID-19.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. Similar to SARS-CoV and MERS-CoV, the SARS-CoV-2 encodes non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein) and accessory proteins. The four non-structural proteins are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus-cell receptor interactions during viral entry. Initial analyses of genomic sequences from SARS-CoV-2 indicate that the catalytic sites of the four SARS-CoV-2 enzymes that could represent key antiviral targets are highly conserved, and share a high level of sequence similarity with the corresponding SARS-CoV and MERS-CoV enzymes.

Most patients with COVID-19 do not require specific antiviral treatment, beyond supportive care. However a subset of approximately 20% may progress to severe pneumonia and about 5% -10% may require critical care. This subset of patients who progress to more severe disease may benefit from early treatment with medications with antiviral activity.

Following our previous interim guidance, remdesivir, a novel nucleotide analogue has received an emergency use authorization, from the United States Food and Drug Administration (FDA), for use in hospitalised patients with severe COVID-19, based on preliminary data from the ACTT-1 trial. Several other important studies for treatments for COVID-19 (remdesivir, lopinavir/ritonavir /interferon-based regimens, hydroxychloroquine, convalescent plasma and dexamethasone) have been published or preliminarily reported since the last review. Key studies informing our recommendations are detailed in Box 1.

Box 1. Key studies informing these therapeutic guidelines

Remdesivir

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med 2020.

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020

Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020.

Hydroxychloroquine

Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020.

Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA 2020.

Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 369:m1849.

Mahevas M, Tran VT, Roumer M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020.

Interferon beta-1B and lopinavir/ritonavir

Hung IF, Lung KC, Tso E, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020.

Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir/ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020; 382:1787.

Convalescent Plasma

Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 (Epub ahead of print).

Duan K, Liu B, Li C, Zhang H, Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020 Apr 6 (Epub ahead of print).

Zeng QL, Yu ZJ, Gou JJ, et al. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. J Infect Dis 2020 Apr 29. (Epub ahead of print).

Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial [published online ahead of print, 2020 Jun 3]. JAMA. 2020;10.1001/jama.2020.10044. doi:10.1001/jama.2020.10044

2. Classification for persons at low versus high risk of disease progression for COVID-19

Low Risk (fulfilling all criterion below)	High Risk (fulfilling any of the criterion below)
Age <30	Age \geq 30, particularly >50
No chronic comorbidities	Chronic comorbidities (chronic lung, heart or kidney disease, diabetes mellitus, immunosuppression, body mass index >25 if age <60)
Reassuring clinical features <ul style="list-style-type: none"> No dyspnoea Respiratory rate \leq 20 breaths/min Normal SpO₂ Not requiring oxygen therapy 	Worrisome clinical features <ul style="list-style-type: none"> Dyspnoea Respiratory rate >20 breaths/min Abnormal SpO₂ (\leq94%) Requiring oxygen therapy
Normal Chest X-ray	Chest X-ray with pneumonia
Reassuring laboratory results* <ul style="list-style-type: none"> CRP \leq 60 mg/L LDH \leq 550 U/L Lymphocytes \geq 1 x 10⁹/L Neutrophils \leq 3 x 10⁹/L 	Worrisome laboratory results <ul style="list-style-type: none"> CRP > 60 mg/L LDH > 550 U/L Lymphocytes < 1 x 10⁹/L Neutrophils > 3 x 10⁹/L

*Certain risk stratification factors may be non-modifiable (e.g. age), whereas others are dynamic (e.g. evolving clinical features, radiology or laboratory results). Repeat laboratory tests are recommended at intervals (e.g. 2-3 days) for patients for whom there is concern for clinical deterioration or when there is worsening of disease. Please note that these cut offs are based on aggregate data from Singapore COVID-19 cases and there may be some variability in normal reference ranges between laboratories

Young et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020; Fan et al. Hematologic parameters in patients with COVID-19 infection. American J of Haematology. Published 4 March 2020; Puah SH et al (ICU data, unpublished)

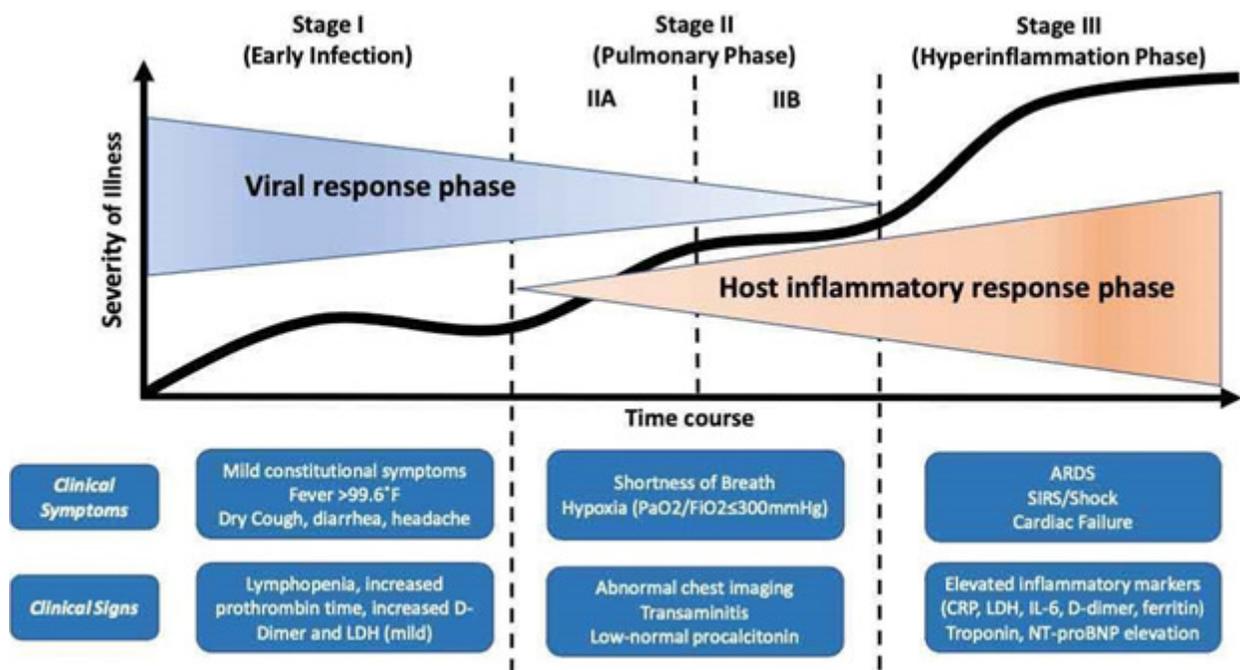
3. Definition of Severe COVID infection (adapted from Report of WHO-China Joint Mission on Coronavirus Disease 2019) – Fulfilling any one of the criterion below

- Dyspnoea, respiratory rate(RR) >30 breaths/min, P/F* ratio <300, Lung infiltrates >50% of lung fields within 24-48 hours
- Admission to an ICU
- Current receipt of mechanical invasive or non-invasive ventilation
- Current receipt of intravenous vasoactive medications to maintain mean arterial pressure >65 mmHg
- Myocarditis/myocardial dysfunction secondary to SARS-CoV-2

Available at: <http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>
 *ratio of PaO₂ to FiO₂

4. Proposed Staging of COVID-19

The staging proposed by Siddiqi et al is a conceptual framework for patients with COVID-19, however bear in mind individual patient’s courses may vary and not all patients enter Stage II or III.



Framework proposed by Siddiqi et al, “COVID-19 Illness in Native and Immunosuppressed States”, J Heart and Lung Transplantation, 2020.

5. Interim Therapeutic Recommendations for COVID-19

I) Level of Recommendations

The level of recommendations are adapted from the Oxford Centre for Evidence-Based Medicine.

Category	Definition
Levels of evidence	
I	Systematic reviews, meta-analyses, well-designed randomized controlled trials (Phase 3)
II	Two groups, non-randomized studies (e.g. cohort, case-control) or early phase (e.g. Phase 2, or which lack sufficient power) randomized controlled trials
III	One-group, non-randomized studies (e.g. before and after, pre-test and post-test)
IV	Descriptive studies that include analysis of outcomes (single-subject design, case series), randomized controlled trials which are not peer reviewed
V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
Grades of evidence	
A	Consistent level I studies
B	Consistent level II or III studies or extrapolations from level I studies
C	Level IV studies or extrapolations from level II or III studies
D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations*	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

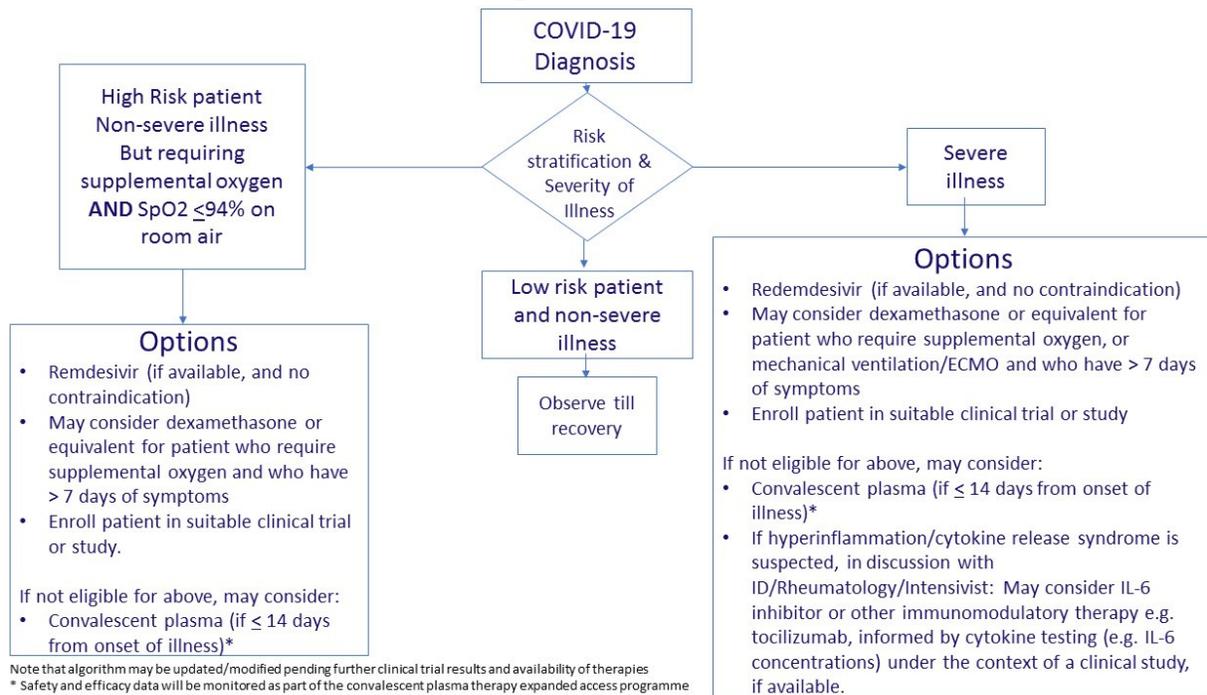
* Recommendations may also be labelled as “conditional”, where the workgroup considers that there are sufficient evidence for desirable effect of adherence to a recommendation probably outweigh the undesirable effects, but is not confident about these trade-off, or is awaiting full peer-review of data.

Most patients with COVID-19 DO NOT require specific antiviral treatment, beyond supportive care.

Specific therapy, however, may be considered for patients predicted to progress to severe infection, or who have severe infection.

These interim recommendations and a treatment algorithm were formulated with the currently available evidence about COVID-19.

II) Interim Treatment Algorithm for COVID-19



III) Recommendations

- 1. We recommend that patients be enrolled in a clinical trial where possible for non-standard therapies, if they meet eligibility criteria (Ungraded).**

Since in most circumstances (except the few highlighted in the following sections), a state of equipoise exists between standard medical care and a proposed therapy, standard medical care, without specific or re-purposed anti-viral therapy, is ethical and adequate. As more definitive knowledge becomes available, however, from COVID-19 therapeutic clinical trials, therapies previously optimally studied under the auspices of a clinical trial may transit to being a standard of care. If a randomised controlled trial (RCT) is available in the institution, and if the patient is eligible, he/she may be enrolled with informed consent. This allows the generation of high-quality evidence for the efficacy and safety of treatments for COVID-19. In keeping with WHO guidance, if treatments are considered outside of clinical trials, certain conditions should be met, including: 1) no proven effective treatment exists or is available and 2) it is not possible to initiate or enrol the patient in a clinical study immediately or 3) data providing preliminary support of the therapy's efficacy and safety are available, at least from laboratory or animal studies, and the use of the therapy outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk-benefit analysis or evidence based guidelines, such as those outlined in this document, and if not covered by this document such therapy be referred to the such an appropriate qualified committee 4) Use of these interventions are in keeping with ethical and off-label medication use policy of the institution;

5) adequate resources are available to ensure that risks can be minimized; 6) the patient's informed consent is obtained and be documented in medical records; and 7) the use of the intervention is monitored and results documented and shared in a timely manner with the wider medical and scientific community¹.

2. We recommend remdesivir for patients with who require supplemental oxygen or have a SpO₂ of \leq 94% or who have severe illness, if available (Level I, Grade A, Moderate).

In vitro data shows remdesivir exerting potent antiviral activity against SARS-CoV-2; [half-maximal effective concentration (EC₅₀) = 0.77 mcgM, half-cytotoxic concentration (CC₅₀) > 100 mcgM. selective index (SI) > 129.87]². Since our last update, three major clinical trials on remdesivir have been published³⁻⁵. One large NIAD RCT ACTT-1 reported preliminary data on 1063 patients (538 remdesivir, 521 placebo), and showed a shortened time to recovery in hospitalised patients with COVID-19 (11 days vs 15 days, $P < 0.001$) based on an eight-point ordinal scale, although no significant 14-day mortality difference was noted (7.1 % with remdesivir vs 11.9% with placebo)³. Inclusion criteria for this trial were one of the following: 1) Radiographic infiltrates on imaging; 2) Oxygen saturation (SpO₂) \leq 94% on room air; or 3) Requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In this study remdesivir seemed more effective when given to patients who were not as severely ill, and in subgroup analyses the time to recovery was significant for the group on supplemental oxygen (but not for those with more severe disease on ECMO, invasive mechanical ventilation or high flow nasal oxygen), or milder disease (not on oxygen). Those with a baseline ordinal score of 5 had a rate ratio for recovery of 1.47 (95% CI 1.17-1.84) compared to 0.95 (95% CI 0.64-1.42) for those with a baseline score of 7. This is hypothesized to be related to the mechanism of action of remdesivir as an antiviral which is usually best given during the viral replicative phase in early illness in COVID-19, prior to clinical worsening (e.g. need for mechanical ventilation). Another study did not find a difference in clinical improvement between a 5-day vs 10-day course of remdesivir for hospitalised patients with COVID-19⁴, although this study was limited in terms of not having a control group, and was thus unable to measure the magnitude of benefit. It should be noted that those receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening were excluded, as were those who had signs of multi-organ failure. A third study with 237 patients in COVID-19 in China did not find a statistically significant different time to clinical improvement, although this trial was felt to be underpowered as it was terminated earlier due to improvement in the COVID-19 situation in Hubei, China and inability to recruit further. This study showed use of remdesivir trended toward shorter duration of illness and mechanical ventilation⁵, although the number of patients were small for the latter. Moving forward it will be important to monitor real world outcomes with the use of remdesivir, outcomes with relation to severity of disease and timing of treatment in relation to onset of illness, and also the full study results of ACTT-1. Also further studies are needed to address combination therapies with remdesivir.

Remdesivir is currently available via clinical trial in Singapore for patients who are eligible. The Health Sciences Authority (HSA) also conditionally approved remdesivir for treatment of COVID-19 in Singapore on 10 June 2020, for adult patients with SpO₂ \leq 94% (room air), or those requiring oxygen supplementation, mechanical ventilation or ECMO, for treatment up to 10 days. Infectious Diseases

(ID) physician approval and request through NCID via the Infectious Diseases consultant-on-call is required. Based on the data by Beigel et al³, we recommend an initial treatment duration of 5 days. This might be extended to 10 days in patients with more severe illness with ID approval.

- 3. If remdesivir is not available, or if there are contraindications to remdesivir, convalescent plasma may be considered for patients requiring oxygen or who have a SpO₂ of $\leq 93\%$ on room air, in particular for patients ≤ 14 days from onset of illness, as part of a monitored expanded access programme (Level II, Grade C, Weak).**

It should be noted that convalescent plasma has not yet been definitively shown to be effective as a treatment for COVID-19. It is available in Singapore as part of a monitored expanded access programme. Shen et al reported good outcomes with convalescent plasma for five patients with COVID-19, however this was a small case series⁶. Following Shen's initial report several other case series on the use of convalescent plasma have been reported with favourable clinical and/or virologic outcomes, but these were also small case series (non-RCTs)⁷⁻⁹. One RCT has been published (103 patients), with a primary outcome of time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale, but this trial was terminated early and was likely underpowered¹⁰. In this study, severe COVID-19 was defined as respiratory distress as indicated by ≥ 30 breaths/min; in resting state, oxygen saturation $\leq 93\%$ on room air; or arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) of 300 or less. Life-threatening COVID-19 was defined as respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring. There was no significant difference in the primary outcome in the convalescent plasma group 51.9% (27/52) vs 43.1%(22/51) in the control group (difference, 8.8% [95% CI, -10.4%to 28.0%]; hazard ratio [HR], 1.40 [95%CI, 0.79-2.49]; P = 0.26). In a post-hoc sub-analysis of those with severe disease, the primary outcome occurred in 91.3 % (21/23) of the convalescent plasma group vs 68.2 % (15/22) of the control group (HR, 2.15 [95%CI, 1.07-4.32]; P = 0.03). No difference was found in the group with life-threatening disease, possibly because the trial was underpowered¹⁰.

While caution should be exercised in convalescent plasma treatment due to the theoretical risk of exacerbating lung injury secondary to immune-enhancement, a pre-print report (not peer reviewed) on key safety metrics after transfusion of ABO-compatible human COVID-19 convalescent plasma in 5,000 hospitalized adults with severe or life-threatening COVID-19 as part of the US FDA Expanded Access Program for COVID-19 convalescent plasma found an incidence of all serious adverse events (SAEs) in the first four hours after transfusion to be $<1\%$, including mortality rate (0.3%)¹¹. There were 25 reported incidences of related SAEs, of which only 2 (of 36) SAEs (transfusion-associated circulatory overload and transfusion-related acute lung injury) were judged as definitely related to the convalescent plasma transfusion by the treating physician. The seven-day mortality rate in this cohort was 14.9%, which was felt to be comparable to the estimated 15-20% mortality in severe COVID-19 in hospitalised patients, lending support that convalescent plasma is at least a safe therapy. Further definitive data on the effectiveness of convalescent plasma as therapy for COVID-19 is awaited.

Inclusion and exclusion criteria for convalescent plasma therapy are listed in Annex A, including the request forms and workflow.

- 4. If remdesivir or convalescent plasma is not available or contraindicated, subcutaneous Interferon beta-1B in combination with lopinavir/ritonavir and ribavirin *may* be considered in early COVID-19, optimally within the context of a clinical study, and preferably a trial if available (Level II, Grade C, Weak).**

In a phase 2 RCT in 125 adults in Hong Kong, combination treatment (lopinavir/ritonavir and ribavirin, with interferon beta-1B if within 7 days of onset of illness, was found to have more rapid nasopharyngeal virologic clearance (7 vs. 12 days) [the study's primary end point], shorter time to symptom alleviation (4 vs. 8 days), and shorter median hospital stay (9 vs. 15 days)¹². In a subgroup analysis, patients in the combination therapy group who did not receive interferon did not have better outcomes than the control group, suggesting that interferon may be the backbone of this treatment, and further studies are planned. Patients had mild COVID-19 in both combination and control groups in this trial, however, as indicated by a median NEWS score of 2.

The LOTUS trial which was a non-blinded RCT on lopinavir/ritonavir monotherapy with 199 patients with more severe COVID-19 (overall mortality 22%), showed that time to clinical improvement did not differ between the two groups (median, 16 days), and the mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25%, -5.8 percentage points; 95% CI, -17.3 to 5.7) but this did not reach statistical significance¹³. In a modified intention-to-treat analysis, which excluded three patients with early death, the between-group difference in the median time to clinical improvement (median, 15 days vs. 16 days) was significant, albeit only very modest (hazard ratio, 1.39; 95% CI, 1.00 to 1.91), and this did not clearly correlate with virologic clearance.

Based on these results we do not recommend lopinavir/ritonavir as monotherapy. This recommendation is also supported by the preliminary results from the RECOVERY and SOLIDARITY trial (WHO) for which peer-reviewed results are awaited. If combination therapy using interferon beta-1B +/- lopinavir/ritonavir is considered, physicians should preferentially enrol patients in a clinical trial, if available. In the circumstance that remdesivir or convalescent plasma is unavailable or contraindicated, and in the absence of a suitable clinical trial, individual physicians, on a case-by-case basis, and in discussion with the patient (or as applicable legal guardian/next-of-kin) and off-label use guidance in their respective institutions, *may* carefully consider the use of interferon beta-1B, lopinavir/ritonavir and ribavirin in early illness (<7 days from onset of illness, who have a NEWS2 score of at least 1)¹⁴. If ribavirin is considered, it should be noted that it is teratogenic and females of reproductive age should be screened for pregnancy prior to its use, and should be advised to avoid pregnancy for six months after treatment with ribavirin. Pregnancy should be avoided for six months in women partners of males who are treated with ribavirin.

- 5. We do not recommend the use of hydroxychloroquine or chloroquine for the treatment of COVID-19 (Level II, Grade B, Moderate) outside of a clinical trial.**

Hydroxychloroquine is less toxic (~40%) than chloroquine in animal data and is widely used in rheumatologic conditions, with in-vitro and in-vivo data for SARS-CoV-2. In vitro Chinese data showed that chloroquine and hydroxychloroquine inhibit SARS-CoV-2, with hydroxychloroquine (EC50=0.72% μ M) found to be more potent than chloroquine (EC50=5.47% μ M)¹⁴.

A small study of 20 COVID-19 patients treated with hydroxychloroquine +/- azithromycin by a French group generated interest as it showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine (in six of 20 patients) was reported to more effectively clear the virus. However numerous concerns were raised with this trial, in particular its open-label and non-randomized nature and small number of patients¹⁵. Following this conflicting data was reported in several small Chinese open label, randomised controlled trials^{16, 17}.

Although one large purported registry study has been retracted due to doubts over the veracity of data¹⁸, several large observational trials have since shown no clear benefit and a potential for cardiac toxicity¹⁹⁻²², in particular when hydroxychloroquine is combined with azithromycin²⁰. Additionally, the RECOVERY Trial interim analysis of 1542 patients who were randomised to hydroxychloroquine, compared with 3132 patients randomised to usual care alone found no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; P =0.10), and no evidence of beneficial effects on hospital stay duration²¹. We therefore do not recommend the use of hydroxychloroquine or chloroquine.

6. We do not currently recommend the use of favipiravir outside of a clinical trial (Ungraded).

Good quality, peer-reviewed data on the clinical efficacy of favipiravir is lacking. There is uncertainty regarding optimal dosing, and its use should be part of a clinical trial.

7. We do not recommend the routine use of immunomodulators, although their use may be considered in select patients with cytokine storm/hyperinflammation, and after careful discussion with multi-disciplinary input (rheumatology-allergy-immunology, infectious diseases, intensive care specialists) (Level IV, Grade C, Weak).

Inhibitors of JAK and IL-6 and other immunomodulators e.g. BTK inhibitors may have a role in select patients with a cytokine release syndrome and immunomodulation in COVID-19 but efficacy is yet to be determined. Examples of such agents include tocilizumab (IL-6 inhibitor) and baricitinib (JAK inhibitors)^{24,25}. Further RCT data is awaited.

- 8. We recommend against the routine use of corticosteroids for COVID-19, except in circumstances where its use is indicated (e.g. refractory shock, documented hypocortisolism). Corticosteroids (dexamethasone 6 mg or equivalent for 10 days) *may* be considered in a subset of patients with more severe COVID-19 (receipt of oxygen, mechanical ventilation and who have symptoms > 7 days) (Level IV, Grade C, moderate, Conditional)**

Prior to results released by the RECOVERY trial, steroids have not been conclusively shown to have specific benefits in COVID-19 infection, and the evidence has been somewhat conflicting²⁶. Studies with reported benefits have been uncontrolled, and confounded by concurrent treatments, and steroids have been known to cause deleterious effects (e.g. bacterial/fungal superinfection) from SARS (2003) data. Steroids will also delay viral clearance, and should be avoided unless there are other reasons for their use such as exacerbation of asthma, COPD and refractory septic shock. The RECOVERY trial results on dexamethasone (pre-print) reported on 2104 patients who were randomised (unblinded) to received dexamethasone (6 mg daily for 10 days) and 4321 patients to standard of care . Patients were eligible if they were hospitalised, and had clinically suspected or laboratory confirmed COVID-19. The trial found that significantly lower mortality patients allocated to dexamethasone (overall 21% vs 24.6%, $P < 0.001$, if on mechanical ventilation 29% vs 40.7%, $P < 0.001$, if on oxygen only 21.5% vs 25.0%, $P = 0.002$, overall $P < 0.01$ for trend)²⁸. Patients with longer duration of symptoms (and thus more likely on mechanical ventilation at randomization) had a reduction in 28-day mortality but not those who had more recent symptom onset (test for trend $P < 0.01$). Based on these results of this trial, and while awaiting its full peer-reviewed publication, dexamethasone 6 mg daily for 10 days (equivalent to prednisolone 40 mg or methylprednisolone 32 mg) *may* be considered in patients with severe COVID-19 requiring supplemental oxygen or mechanical ventilation who have a symptom onset of > 7 days, and who do not have contraindications to such treatment (Conditional recommendation) ²⁷.

- 9. We do not recommend the use of other therapies such as mesenchymal stem cell infusion or donor lymphocyte infusions due to the lack of robust data on efficacy in COVID-19 (Ungraded).**
- 10. We do not recommend post-exposure chemoprophylaxis for COVID-19 with hydroxychloroquine (Level 1, Grade A, Strong). We do not recommend pre-exposure chemoprophylaxis for COVID-19 outside of a clinical trial (Ungraded).**

One RCT involving 821 subjects found no benefit with post-exposure prophylaxis²⁸, although this study had some limitations (only just over 10% of COVID-19 cases confirmed by PCR, and a delay of 3 or more days between exposure and starting preventive treatment. Pre-exposure trials are underway (e.g. Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] trial, involving 15,000 health care workers; ClinicalTrials.gov number, NCT04334148).

11. We recommend the use of pharmacological venous thromboembolism (VTE) prophylaxis for critically ill patients with COVID-19 or for those with severe disease (e.g. patients in intensive care, or who are hypoxic requiring supplemental oxygen and are non-ambulant). If pharmacological prophylaxis is contra-indicated, mechanical prophylaxis is recommended (Level 1, Grade A, Strong).

This recommendation represents good clinical practice in the intensive care setting, and is in keeping with international guidelines^{29,30} based on RCTs which in absolute and relative terms, have demonstrated that pharmacological prophylaxis reduces mortality, pulmonary embolism, and deep vein thrombosis. COVID-19 is associated with thromboembolic disease as a result of various factors, including endothelitis associated with COVID-19, an increase in circulating prothrombotic factors, and immobility in critical illness^{31, 32}. PT/PTT, Fibrinogen and D-dimer may be assessed prior to commencement of pharmacologic prophylaxis. Higher rates of thrombosis are seen in ICU COVID-19 patients, in studies that systematically evaluate for them³³⁻³⁶. The International Society on Thrombosis and Haemostasis (ISTH) Interim Guidance (21 Mar 2020) recommends that prophylactic low molecular weight heparin (LMWH) should be considered in all (including non-critically ill) patients if they require hospital admission for COVID-19³⁷. However more data is awaited for this recommendation in non-critically ill patients and in different ethnic cohorts.

Please note that the recommendations above are based on current data, and that updates will be made to this guidance as more evidence becomes available. Attempts should be made to conduct randomised clinical trials to validate treatment protocols. Off-label usage of the above drugs outside of a trial should be monitored so as to accrue real time data that could facilitate analysis of treatment outcomes and any adverse events. **Clinical evidence summaries for various therapeutics for COVID-19 are also available from the Ministry of Health-Agency for Care Effectiveness at <https://www.moh.gov.sg/covid-19/clinical-evidence-summaries> and US-NIH <https://www.covid19treatmentguidelines.nih.gov/>.**

References

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6. Key Drug Summary Table (Note: Therapy should be guided by a Infectious Diseases Physician)

Medication	Adult Dose	Notes (Please see full product information leaflet/drug use guide)
Use as clinically available per institutional policy or as part of a clinical trial		
Remdesivir	200 mg IV loading, 100 mg IV daily x 5 to 10 days	As part of clinical trial (See Annex B) or as clinically available Timing of antiviral initiation may be important, as administration with high viral loads seen after peak viral titre has been found to fail in reducing lung damage despite reducing viral loads. Early therapy may be more beneficial compared to later therapy. May cause LFT abnormalities/hepatitis. Monitor LFTs prior to initiation and regularly while on remdesivir.
Dexamethasone	6 mg PO or IV	Dose: 6 mg oral or IV for 10 days. If dexamethasone is unavailable, may consider substitution with equivalent daily doses of another corticosteroid (e.g. methylprednisolone 32 mg, prednisolone 40 mg). Do NOT use dexamethasone in patients without hypoxemia requiring oxygen. Caution in patients with concurrent infections. Monitor for hyperglycaemia.
Drugs used optimally in the context of a clinical trial (if off-label use, per institutional policy and with careful discussion and monitoring)		
Lopinavir/ritonavir	400/100 mg BD x 14 days Use syrup if intubated/unable to swallow.	Assess for drug-drug interactions. Main side effect is gastrointestinal intolerance and hepatitis. Monitor LFTs. Duration may be shortened if clinically improved, being discharged, or dose limiting side effects are encountered. Caution against monotherapy; trials have studied it in combination with interferon beta-1B in early COVID-19 (week 1 of illness)
Interferon Beta-1B	250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected subcutaneously every other day up to 7-14 days (3-7 doses).	If the patient has had significant improvement within 1 week (e.g. normalization of P/F ratios, no need for supplemental oxygen, patient extubated), clinicians may consider a shorter course of therapy (e.g. 3 doses, or 1 week). Consider use in combination with lopinavir/ritonavir. Common side effects: Flu-like symptoms It has been studied in COVID-19 within 7 days from onset of illness). Caution should be exercised in starting interferon in later stages of COVID-19 (e.g. when there is ARDS secondary to the established inflammatory cytokine cascade).
Ribavirin	400 mg BD x 14 days	If ribavirin is considered, it should be noted that it is teratogenic and females of reproductive age should be screened for pregnancy prior to its use, and should be advised to avoid pregnancy for six months after treatment with ribavirin. Pregnancy should be avoided for six months in women partners of males who are treated with ribavirin. Monitoring parameters: Pre-treatment FBC/Renal panel/LFTs, ECG, urine pregnancy test (females)
Tocilizumab	Dose is typically 8 mg/kg, may be repeated 24 hours later. To discuss with Rheumatology-Allergy-Immunology / Infectious Diseases /Intensive Care Physicians	
Convalescent plasma	Request via ID physician-on-call (NCID/TTSH). The standard dose of CP for adults to be administered is 500 mls as a single dose over 1-2 hours. The dose of CP for children is 4-5 ml/kg as a single dose over 1-2 hours.	

Annex A

SPECIFIC INFORMATION ON REMDESIVIR (GS-5734)

Originally developed to combat Ebola and Marburg virus infections, remdesivir is a prodrug that is metabolized intracellularly to an analogue of adenosine triphosphate that inhibits a key viral enzyme, the RNA-dependent RNA polymerase, and shuts down viral replication. *In vitro* data and effects in animal models support its development as a potential pan-coronavirus antiviral based on result against SARS-CoV and MERS-CoV.¹⁻⁵

Given the initial absence of specific antiviral therapy for COVID-19 and its ready availability as a potential antiviral agent, remdesivir was identified early as a promising therapeutic candidate for COVID-19.

Summary of evidence

COVID-19

Remdesivir proves to be a potent inhibitor of SARS-CoV-2 *in vitro*. In Vero E6 cells, remdesivir inhibited SARS-CoV-2 with a 50% effective concentration (EC₅₀) of 0.77 µM.⁶ In human nasal and bronchial airway epithelial cells, daily treatment with remdesivir resulted in over 7.0 log₁₀ reductions of intracellular SARS-CoV-2 viral titres at 48 hours post-infection.⁷

In a rhesus macaque model of SARS-CoV-2 infection, animals treated with remdesivir did not show signs of respiratory disease and had reduced pulmonary infiltrates on radiograph compared to vehicle-treated animals.⁸ Virus titres in bronchoalveolar lavages were significantly reduced as early as 12 hours after the first treatment was administered. At necropsy on day 7 after inoculation, lung viral loads of remdesivir-treated animals were significantly lower with reduction in damage to the lung tissue.

Published non-comparative studies and case reports have generally described improvement in clinical status in patients after initiation of remdesivir.⁹⁻¹³ Preliminary results from a randomised controlled trial of 1,063 patients with COVID-19 and evidence of lower respiratory tract infection found that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI] 9 to 12) versus 15 days (95% CI 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI 1.12 to 1.55; p<0.001).¹⁴ Notably, almost 89% of the patients had severe disease at enrolment. The Kaplan-Meier estimates for mortality at 14 days were not significantly different—7.1% with remdesivir and 11.9% with placebo (hazard ratio [HR] for death, 0.70; 95% CI 0.47 to 1.04). Mortality rates at 28 days are pending as a large proportion of patients are yet to complete the trial. The authors highlighted the need to start antiviral treatment before the pulmonary disease progresses to require mechanical ventilation.

In contrast, another randomized trial from China in which 237 patients were enrolled (158 assigned to remdesivir and 79 to placebo), the time to clinical improvement was 21.0 days (interquartile range [IQR] 13.0 to 28.0) in the remdesivir group and 23.0 days (IQR 15.0 to 28.0) in the control group, with a hazard ratio (for clinical improvement) of 1.23 (95% CI, 0.87 to 1.75). 28-day mortality was similar between the two groups (22 [14%] died in the remdesivir group versus 10 [13%] in the placebo group; difference of 1.1% [95% CI -8.1 to 10.3]).¹⁵ Of note, this trial was prematurely terminated before reaching the pre-specified sample size (owing to the end of the outbreak) and had insufficient power to detect differences in clinical outcomes.

An open-label phase 3 trial evaluating a 5-day versus 10-day regimen in 397 patients with severe COVID-19 not requiring mechanical ventilation demonstrated that by day 14, a clinical improvement of 2 points or more on a 7-point ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group.¹⁶ After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group ($p=0.14$). In addition, no new safety signals were identified. The study has been expanded and a similar trial will compare the regimens in patients with moderate COVID-19.

Benefits

Usage of remdesivir is not routinely recommended for all patients with COVID-19, but its use may be considered, for patients who have or who are anticipated to develop severe pulmonary disease. Remdesivir may be available by prescription or else part of a clinical trial.

Dosage

Intravenous remdesivir at 200mg loading dose on day 1, followed by 100mg daily maintenance dose for 5 days, this may be extended up to 10 days.

Harms

Infusion-related reactions have been observed during, and/or have been temporally associated with, administration of remdesivir. Signs and symptoms may include diaphoresis, hypotension, nausea, vomiting, and shivering have been observed. Discontinue administration and institute appropriate treatment if a clinically significant infusion reaction occurs.¹⁷

Transaminase elevations have been observed in healthy volunteers and patients with COVID-19. Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline and should be discontinued in patients who develop ALT ≥ 5 times the upper limit of normal or who experienced ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and regularly while receiving remdesivir dosing (Note: The ACTT-1 trial monitored liver function tests on day 1; 3, 5, 8, 11 of administration, FDA recommends daily liver function test monitoring, incidence of transaminitis was 4.1% in Remdesivir arm and 7.3% in placebo arm in the ACTT-1 trial).¹⁷

Additional Considerations

Drug formulation contains the excipient sulfobutylether β -cyclodextrin sodium (SBECD). Renal tubular vacuolation and hypertrophy are both previously described changes associated with its administration in non-human species.¹⁸ Because SBECD is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD is not recommended in patients with moderate to severe renal impairment unless the benefit of therapy outweighs the risk. Additionally, there is no safety or pharmacokinetic data available for patients with kidney impairment or patients who require renal replacement therapies.

Conclusions

Preliminary RCT results shows faster recovery for patients with severe COVID-19 who received remdesivir compared with placebo. Identifying the shortest duration of effective treatment with remdesivir could reduce length of hospitalisation and bed occupancy, reduce possible side effects as well as extend the scarce supply of remdesivir available. Further clinical trial results are needed to build on the current available evidence and guide its use, alone or in combination with other antivirals, for varying degrees of illness severity.

SPECIFIC INFORMATION ON LOPINAVIR/RITONAVIR AND INTERFERON BETA-1B

Lopinavir/ritonavir (Kaletra)

Lopinavir is licensed as a human immunodeficiency virus 1 (HIV-1) protease inhibitor that is co-formulated with ritonavir to increase lopinavir half-life through the inhibition of cytochrome P450. Lopinavir/ritonavir (LPV/r) are hypothesized to exhibit anti-CoV activity by inhibit the 3-chymotrypsin-like protease of SARS and MERS,¹⁹ which is a key enzyme in CoV polyprotein processing. LPV and/or LPV/r have anti-CoV activity *in vitro*, as well as in MERS-CoV-infected non-human primates and in non-randomised trials of SARS patients.¹⁹⁻²³

Summary of evidence

SARS

A previous study on the sequential changes in viral load and disease progression of SARS suggested that there was an initial viral replicative phase that led to a maximal viral load at around day 10. Thereafter, the disease progressed to ARDS and severe end-organ damage in some patients.²⁴ Using the strategy to reduce the peak viral load by an effective antiviral agent, a retrospective matched cohort study showed that the addition of LPV/r as an initial treatment (median, 5.5 days after symptom onset) for patients newly diagnosed to have SARS was associated with a reduction in overall death rate (2.3%) and intubation rate (0%) compared with that in a matched cohort who received standard treatment of ribavirin (15.6% and 11.0% respectively, $p < 0.05$), and a lower rate of use of methylprednisolone at a lower mean dose.¹⁹ However, when LPV/r was given as rescue therapy later in the course of illness (median, 18 days after symptom onset) when patients had worsening oxygen saturation, shortness of breath, and relevant radiological findings, and were judged to have failed pulse steroid treatment, there was no difference in overall death rate and rates of oxygen desaturation and intubation compared with the matched cohort.¹⁹

Another retrospective matched cohort study found that the adverse clinical outcome (acute respiratory distress syndrome or death) was significantly lower when LPV/r was added to the treatment regimen compared to the controls (2.4% v 28.8%, $p < 0.001$) at day 21 after the onset of symptoms. In addition, the LPV/r group had a progressive decrease in the viral load, an early rise in the lymphocyte count, a reduction in the cumulative dose of pulsed methylprednisolone, and fewer episodes of nosocomial infections.²⁰ In the subgroup analysis, patients who received LPV/r as the initial treatment seemed to run a milder disease course and had a reduction in the viral load. Their need for rescue pulse methylprednisolone for severe respiratory deterioration was therefore reduced. The authors hypothesized that LPV/r might have improved the outcome either by a direct effect on the viral load or by an indirect steroid sparing effect because of a reduction in immunopathological damage.²⁰

MERS

Although the antiviral activity of LPV against MERS-CoV has been reported in Vero cells, other studies report complete inactivity.^{21,25} Another *in vitro* study reports that LPV/r has inferior *in vitro* antiviral

activity compared to remdesivir and interferon beta.²⁶ In mice, therapeutic LPV/r and interferon beta combination improved pulmonary function, but failed to reduce viral replication or severe lung pathology.²⁶ Common marmosets that were treated with LPV/r or interferon beta-1b had better clinical scores, less weight reduction, less pulmonary infiltrates, and improved pathological findings. Furthermore, necropsied lung and extrapulmonary tissues from the treated group had lower mean viral loads.²² The combination of both LPV/r and interferon beta-1b is being tested in a randomized control trial in Saudi Arabia among patients with MERS.²⁷ Apart from this, experience in humans till date is limited to two case reports of successfully treating MERS-infected patients with LPV/r, ribavirin and interferon.^{28, 29}

COVID-19

Four patients with COVID-19 were given LPV/r combined with Chinese medicine treatment. After treatment, three patients showed significant improvement in pneumonia associated symptoms, two of whom were confirmed to be COVID-19 negative and discharged, and one of whom was negative for the virus at the first test.³⁰ Locally, five patients were treated with LPV/r within 1 to 3 days of desaturation, but evidence of clinical benefit was equivocal.³¹ While defervescence occurred within 1 to 3 days of LPV/r initiation, it was unable to prevent progressive disease in 2 patients. Decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs also appeared similar between those treated and not treated with LPV/r.

A randomized, controlled, open-label trial of 199 hospitalized COVID-19 adult patients with more severe disease (patients who were eligible: oxygen saturation \leq 94% or less on room air or PaO₂:FiO₂ < 300 mm Hg) were randomized to receive LPV/r for 14 days in addition to standard care (n=99), or standard care alone (n=100).³² Time to clinical improvement did not differ between the two groups (median, 16 days), except in a modified intention-to-treat analysis, which excluded 3 persons with early death (15 vs 16 days, hazard ratio [HR] 1.39; 95% confidence interval [CI] 1.00 to 1.91). In the intention-to-treat population, LPV/r treatment within 12 days after the onset of symptoms was not found to be associated with shorter time to clinical improvement (HR 1.25; 95% CI 0.77 to 2.05); similar results were found regarding later treatment with LPV/r (HR 1.30; 95% CI 0.84 to 1.99). There was also no significant difference in mortality between the two groups, although the mortality rate at 28 days was numerically lower with LPV/r compared with standard care (19.2% vs 25% , -5.8 percentage points; 95% CI -17.3 to 5.7).

The ELACOI trial conducted in 86 patients with mild to moderate COVID-19 reported no significant difference in time to undetectable viral RNA load between patients who received LPV/r in addition to standard care versus umifenovir (Arbidol) in addition to standard care versus standard of care alone (mean 9 days).³³

Benefits

Usage of LPV/r is not routinely recommended for all patients with COVID-19, but its use may be considered, in combination with interferon beta-1b and ribavirin, for patients who are anticipated to develop severe disease, and who are in early phase of illness (\leq 7 days from onset), who are not candidates for remdesivir or convalescent plasma.

Harms

Diarrhoea, nausea, and asthenia are the most frequently reported reactions in patients receiving LPV/r therapy.³⁴ Elevated total cholesterol, triglyceride and hepatic enzyme levels, as well as pancreatitis have also been reported.³⁵ Symptoms and laboratory tests returned to normal after LPV/r therapy was ceased.

LPV/r is recommended to be used with caution in patients with Hemophilia A or B, hepatic impairment or underlying hepatic disease, as well as patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies.³⁵

Additional Considerations

There are a number of clinically important drug interactions that have been reported with LPV/r use, necessitating dosage adjustments of interacting drugs and/or LPV/r, and several other drugs are which contraindicated with concomitant LPV/r. We strongly recommend to consult a drug interaction database (such as www.covid19-druginteractions.org) or a pharmacist.

LPV/r has the potential to interact with certain drugs (such as flecainide, propafenone, midazolam, and triazolam) that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Co-administration with LPV/r is also not recommended for drugs (such as rifampicin) that may substantially reduce LPV plasma concentrations, or drugs whose plasma concentrations elevated by LPV/r may lead to serious adverse reactions (such as simvastatin and lovastatin). To reduce the risk of their toxicity when co-administered with LPV/r, the recommended actions include: (i) monitoring of the drug plasma concentration; (ii) the use of alternative agents; (iii) dosage adjustments.³⁶

LPV/r tablets are to be swallowed whole, not to be chewed or crushed. Exposure of lopinavir can be reduced by 45% when the tablet is crushed.³⁵ The syrup formulation of LPV/r contains propylene glycol (15.3%) and alcohol (42% v/v) and is not recommended for use with polyurethane feeding tubes due to incompatibility and also should not be given to pregnant women, or co-administered with drugs capable of producing disulfiram-like reactions (e.g. metronidazole).³⁵

Conclusions

Limited evidence published till date on LPV/r do not support its routine use for patients with COVID-19. Further trials are needed to help confirm or exclude the possibility of a treatment benefit.

Interferon beta-1b

Interferon beta-1b is a cytokine that is licensed for use in the treatment of relapsing multiple sclerosis. It is a type I interferon, and is a signalling protein made and released by host cells in response to the presence of several viruses, that help regulate the activity of the immune system.

The host innate interferon response is crucial for the control of viral replication after infection. Although CoVs are able to suppress the interferon response for immune evasion, they remain susceptible to interferon treatment *in vitro*. The interferon response can be augmented by the administration of recombinant interferons or interferon inducers. Antiviral effects of type I interferons have been demonstrated in monkey (Vero; Vero-E6), fetal rhesus monkey kidney (fRhK-4) and human (Caco2, CL14, and HPEK) cell lines.³⁷

Various combinations of interferon alfa or interferon beta used alone or with other antivirals have been used to treat patients with SARS or MERS.

Summary of evidence

SARS

In an uncontrolled open-label study of 22 SARS patients, the interferon alfacon-1 treatment group had a shorter time to 50% resolution of lung radiographic abnormalities, had better oxygen saturation, resolved their need for supplemental oxygen more rapidly, had less of an increase in creatine kinase levels, and showed a trend toward more rapid resolution of lactate dehydrogenase levels compared with the group receiving corticosteroids alone.³⁸

Although interferon beta was shown to be superior to interferon alpha or interferon gamma in *in vitro* study of the SARS-CoV,³⁹⁻⁴³ there are no studies using interferon beta on SARS patients.

MERS

In vitro studies showed superiority of interferon beta compared to interferon alpha-2b, interferon-gamma, interferon universal type 1 and interferon alpha-2a in reducing MERS-CoV replication.^{25, 44} A recent study published showed that interferon beta demonstrated superior antiviral activity to LPV/r *in vitro*, and the antiviral activity of LPV/r and interferon beta combination on MERS-CoV is dominated by interferon beta when LPV/r is used at clinically relevant concentrations.²⁶ In mice, therapeutic LPV/r and interferon beta improves pulmonary function but does not reduce virus replication or severe lung pathology.²⁶ A study done in common marmosets showed that interferon beta-1b improvements in clinical outcomes.²²

In a cohort study of 51 patients, the use of interferon beta demonstrated improved survival in patients treated with interferon beta in the univariable analysis, but the multivariable analysis which included a marker of severity of illness did not show an association between treatment with interferon beta and survival and could have been because interferon beta was given to less severely ill patients.⁴⁵

Since interferon beta was shown to be the most potent against MERS-CoV *in vitro*, it was selected to use in the randomised control trial (MIRACLE trial) in combination with LPV/r to determine if this combination improves clinical outcomes in MERS-CoV patients.⁴⁵

COVID-19

A phase 2, open-label, randomised trial conducted in 127 patients compared combination therapy (LPV/r, ribavirin, and subcutaneous interferon beta-1b) with standard of care versus LPV/r monotherapy with standard of care.⁴⁶ The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; HR 4.37 [95% CI 1.86–10.24], p=0.0010). Clinical improvement, as measured by the National Early Warning Score 2 (NEWS2), were similarly improved, with patients in the combination therapy arm reporting statistically significantly shorter time to complete alleviation of symptoms compared to patients in the LPV/r monotherapy arm (4 days vs 8 days, p<0.0001), resulting in a significantly reduced median length of hospital stay of 5.5 days (9 days vs 14.5 days, p=0.016).

Benefits

Usage of interferon beta is not routinely recommended for all patients with COVID-19, but its use may be considered, possibly in combination with LPV/r and ribavirin, for patients who are anticipated to develop severe pulmonary disease, and who are in early phase of illness (≤ 7 days from onset of illness), who are not candidates for remdesivir or convalescent plasma.

Dosage: Subcutaneous interferon beta-1b 250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected every other day for up to 7-14 days (3-7 doses). If the patient has had significant improvement within 1 week (e.g. normalization of P/F ratios, no need for supplemental oxygen, patient extubated), clinicians may consider a shorter course of therapy (e.g. 3 doses, or 1 week).

Harms

As the dosage regimen recommended does not have a dose titration step at the start of treatment, close monitoring is required.

Injection site reactions occurred frequently after administration of interferon beta. Flu-like symptoms have been seen. Rarely, monoclonal gammopathy patients treated with interferon beta-1b may develop systemic capillary leak syndrome.⁴⁷ Other uncommon side effects include hypersensitivity, pancreatitis, depression, cytopenia, cardiomyopathy, and liver and thyroid dysfunction.⁴⁷

Additional Considerations

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when interferon beta is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance (e.g. anti-epileptics). Additional caution should be exercised with any co-medication which has an effect on the haematopoietic system. No interaction studies with anti-epileptics have been carried out.

Interferon beta should be used with caution in patients with bone marrow suppression, cardiovascular disease, seizure disorder, hepatic impairment, thyroid dysfunction, severe renal failure, history of depression. It is contraindicated for use in pregnancy, patients with current severe depression and/or suicidal ideation, patients with decompensated liver disease.

Conclusions

With limited experience from *in vitro*, animal and human studies, interferon beta-1b alone or in combination may be considered as a potential treatment option for COVID-19. Results from ongoing randomised controlled trials have been initiated to test its efficacy.

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Annex B: Indications and Contraindications to Convalescent Plasma therapy

The indications for CP administration are as follows (adapted from WHO severe disease criterion and Arabi et al)¹:

Laboratory-confirmed COVID-19 Infection AND 1) or 2)

1) Severe or Critical illness as defined by:

WHO Criterion

- a. Dyspnea
- b. RR>30/min
- c. SaO₂ ≤93%
- d. P/F ratio <300
- e. Lung infiltrates >50% of lung fields within 24-48 hours

Other criterion

- a. Admission to an ICU
- b. Current receipt of mechanical invasive or non-invasive ventilation
- c. Current receipt of intravenous vasoactive medications to maintain mean arterial pressure >65 mmHg
- d. Myocarditis/ myocardial dysfunction secondary to SARS-CoV-2

OR

2) Predicted progression to severe illness as defined by:

Need for supplemental oxygen /dyspnoea / respiratory rate >20/min AND one of the following:

- a. Marked lymphopenia (<1.0 x 10⁹/L)
- b. Neutrophilia (>3.0x10⁹/L)
- c. Markedly raised and increasing levels of CRP (>60 mg/L)
- d. LDH (> 550 U/L)
- e. Rising Ferritin
- f. D-dimer >1 mcg/ml
- g. Elevated troponin
- h. Progressive lung infiltrates, or a validated predictive model (Reference 6, 7).

Exclusion criteria:

- a. Symptomatic illness exceeding two weeks (14 days) at time of enrolment.
- b. History of allergic reaction to blood or plasma products
- c. Known IgA deficiency (IgA levels should be checked prior to transfusion, levels should not be below reference interval).
- d. Medical conditions in which receipt of 500 mL intravascular volume may be detrimental to the patient (e.g., actively decompensated congestive heart failure).

Requests for convalescent plasma should be made via the Infectious Diseases Physician on call, NCID/TTSH through the TTSH Operator at 63571000.

¹ Available at: <http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>;
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Affix Patient Label

Patient Name:

Patient NRIC:

Request Form for Novel Treatment with Convalescent Plasma Transfusion for COVID-19 Infection

Patient Clinical Information (*Please tick and circle accordingly)

Date of COVID-19 (novel coronavirus) confirmation: _____
(i.e. Positive swab)

Date of Onset Illness: _____

Date of ICU admission: _____
(if applicable)

Clinical Feature	Yes	No	Clinical Feature	Yes	No
Dyspnoea	<input type="checkbox"/>	<input type="checkbox"/>	On vasopressors	<input type="checkbox"/>	<input type="checkbox"/>
Respiratory rate >30	<input type="checkbox"/>	<input type="checkbox"/>	Marked lymphopenia (<1.0 x10 ⁹ /L)	<input type="checkbox"/>	<input type="checkbox"/>
Arterial oxygen saturation (SaO ₂) <93%	<input type="checkbox"/>	<input type="checkbox"/>	Neutrophilia (>3.0 x10 ⁹)	<input type="checkbox"/>	<input type="checkbox"/>
PaO ₂ /FiO ₂ (P/F ratio) <300	<input type="checkbox"/>	<input type="checkbox"/>	Serum Lactate Dehydrogenase (LDH) > 550 U/L	<input type="checkbox"/>	<input type="checkbox"/>
Lung infiltrates >50% within 24-48 hours	<input type="checkbox"/>	<input type="checkbox"/>	D-dimer > 1 mcg/ml	<input type="checkbox"/>	<input type="checkbox"/>
Intensive care unit (ICU) patient	<input type="checkbox"/>	<input type="checkbox"/>	Elevated troponin	<input type="checkbox"/>	<input type="checkbox"/>
Mechanical ventilation	<input type="checkbox"/>	<input type="checkbox"/>	Suspect or confirmed myocarditis/myocardial dysfunction	<input type="checkbox"/>	<input type="checkbox"/>

Other Comments on Current Clinical Status:

Blood Group: _____ A / B / O / AB Rhesus Positive / Negative

Serum Immunoglobulin A (IgA) levels: _____
(please include units)

History of Allergic Reactions to Blood Products: _____
(If Yes, please elaborate)

Clinical Trials Enrolled in (if any), please include intervention(s) if known (e.g. Open label):	
*Other COVID-19 Related Therapy (if any): _____	
Patient / Next-of-kin Agreeable in-Principle: Yes / No	
Requestor Details	
Name of Hospital / Organisation:	Name and MCR No. of Requesting Physician:
Date of Request:	Signature:

- Refer to Annex 4 Procedure Information Sheet for Novel Treatment with Convalescent Plasma Transfusion for COVID-19 Infection
- Email this form to: Clinical Director NCID (shawn_vasoo@ncid.sg) and cc to HOD TTSH Haematology (kiat_hoe_ong@ttsh.com.sg); and please TigerText information simultaneously. If no response within 24 hours please contact ID consultant on call 63571000 via TTSH operator. If urgent please indicate in email or TigerText, and if no response within 2 hours, please call ID consultant on call.

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